# The biocompatibility of neutral pH, low-GDP peritoneal dialysis solutions: benefit at bench, bedside, or both?

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**For patients on peritoneal dialysis (PD), the development of peritonitis, the decline of residual kidney function, and the loss of peritoneal membrane function are central events that affect both patient and technique survival. The use of glucose as the osmotic agent in conventional PD solutions may increase the susceptibility to each of these events. However, its use may also be associated with systemic metabolic perturbations and, in turn, an increase in cardiovascular morbidity. Both *in vitro* and *in vivo* evidence suggest that both the local peritoneal and systemic toxicity induced by the use of glucose may be in part mediated by the presence of glucose degradation products (GDPs) coupled with the hyperosmolarity, reduced pH, and use of lactate as the buffer in conventional PD solutions. Therefore, the use of neutral pH, low-GDP ($NpHL_{GDP}$), bicarbonate-buffered PD solutions may represent a promising strategy to attenuate some of these adverse effects. However, the impact of these novel solutions on clinical outcomes remains largely unknown. In this review, we will highlight evidence regarding the biocompatibility of $NpHL_{GDP}$ PD solutions, review the utility of current biomarkers in the evaluation of biocompatibility, and discuss the clinical outcome data with these solutions.**

*Kidney International* (2011) **79,** 814–824; doi:10.1038/ki.2010.515; published online 19 January 2011

KEYWORDS: advance glycosylation end products; biocompatibility; glucose degradation products; peritoneal dialysis solutions; peritoneal membrane; residual kidney function

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**Received 31 July 2010; revised 3 October 2010; accepted 20 October 2010; published online 19 January 2011**

Central to the success of peritoneal dialysis (PD) is the long-term preservation of the peritoneal membrane. In contrast to hemodialysis (HD) in which the specifications of the dialyzer are known and can be altered, the peritoneal membrane is a biological membrane and susceptible to injury. Peritoneal membrane changes seen with increasing duration on PD include fibrosis, and both quantitative and qualitative changes within the peritoneal microcirculation.[1] These changes correlate with increasing small-solute permeability and a reduction in peritoneal ultrafiltration (UF) capacity,[2,3] and may be partially responsible for the shortened technique survival of PD relative to HD.[4,5]

The observation that these deleterious changes occurred under conditions of chronic exposure to conventional hyperosmolar glucose-containing, lactate-buffered, low-pH PD solutions has led to the conclusion that the composition of conventional PD solutions is responsible. If dialysate incompatibility contributes to technique failure, then manipulation of conventional PD solution composition represents a therapeutic target to improve patient outcomes on PD. Possible strategies include the use of non-glucose-based PD solutions, or, alternatively, modification of other dialysate components to minimize the local peritoneal and systemic toxicity imposed by glucose. The latter strategy involves the use of glucose-based, neutral pH, low glucose degradation product ($NpHL_{GDP}$) PD solutions to minimize the toxicity mediated by GDPs and low pH. Both *ex vivo* and animal data provide convincing evidence that peritoneal and systemic exposure to GDP and low pH have been linked to peritoneal membrane injury, impairment of local peritoneal host defenses, renal injury, and systemic inflammation.

We will summarize the current knowledge regarding the bioincompatibility of conventional PD solutions, while highlighting the variability in the composition of commercially available, $NpHL_{GDP}$ PD solutions. The impact of these solutions on clinical outcomes, including peritoneal membrane function, preservation of residual kidney function

(RKF), PD-related infectious complications, as well as patient and technique survival will be presented.

## PRODUCTION OF LOW-GDP, NEUTRAL pH SOLUTIONS

Heat (autoclave) sterilization of conventional glucose-based PD solutions has given rise to elevated levels of dialysate GDPs that are produced during both manufacturing and storage.[6,7] To reduce this caramelization of glucose, it is buffered with lactate and the solution is maintained at a low pH (5.0–6.0).[6] In contrast, $NpHL_{GDP}$ PD solutions have a final pH of approximately 6.2–7.4. The use of a multi-bag system allows for separation into two compartments: a low-pH glucose compartment, which minimizes the production of GDPs during heat sterilization and storage,[8,9] and a buffer compartment, which can be lactate, a bicarbonate/lactate mixture, or bicarbonate alone (Table 1). This also separates calcium from bicarbonate, avoiding precipitation of the two until both compartments are mixed immediately before instillation. The final GDP content and type varies by solution and manufacturer[10] (Figure 1).

**Table 1 | Commercially available, neutral pH, low-GDP peritoneal dialysis solutions and conventional peritoneal dialysis solution**

| | | Buffer (mmol/l) | | |
|---|---|---|---|---|
| | Chambers | Lactate | Bicarbonate | Final pH |
| Balance | 2 | 35 | — | 6.8 |
| Bicavera | 2 | — | 34/39 | 7.1 |
| Gambrosol Trio | 3[a] | 39–41 | — | 6.5 |
| Physioneal | 2 | 10/15 | 25 | 7.3 |
| Conventional | 1 | 35/40 | — | 5.0–5.4 |

Abbreviation: GDP, glucose degradation product.
[a]Chambers to allow for final glucose concentration of three different concentrations.

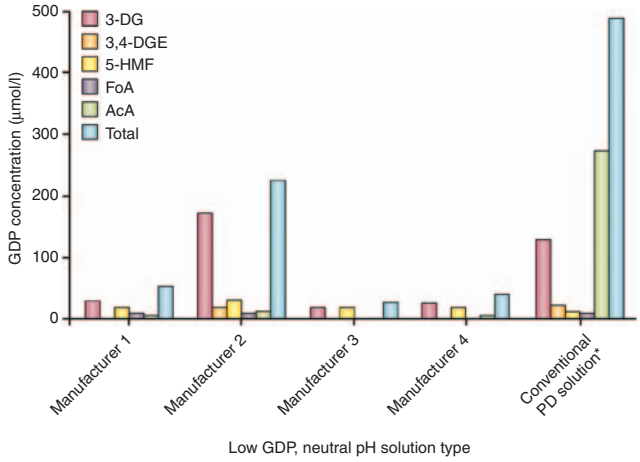


**Figure 1 | The GDP content among commercially available neutral pH, low-GDP peritoneal dialysis solutions (solutions 1–4) compared with the GDP content of conventional peritoneal dialysis solutions (solution 5).** Adapted from Erixon M. *et al.*[10] 3-DG, 3-deoxyglucosone; 3,4-DGE, 3,4-dideoxyglucosone-3-ene; 5-HMF, 5-hydroxymethyl furaldehyde; AcA, acetaldehyde; FoA, formaldehyde; GDP, glucose degradation product. *GDP concentrations for conventional peritoneal dialysis solutions (solution 5) were taken as an average from published values for Gambrosol, StaySafe, and Dianeal. All solutions are prepared using a commercially available 2.5% glucose concentration peritoneal dialysis solution. Total GDP content as measured by the summation of the individual glucose degradation products measured.

## LOCAL 'BIOINCOMPATIBILITY' OF CONVENTIONAL PD SOLUTIONS

### Glucose

Uremia initiates structural peritoneal membrane changes that are exacerbated with increasing duration on PD.[1] Peritoneal biopsy registry data suggest that these changes are seen across all resident cells of the peritoneum.[1] These changes include the loss of the mesothelial monolayer, thickening of the submesothelial compact collagenous zone, neovascularization, and additional vascular changes including subendothelial hyalinization of post-capillary venules, with accompanying obliteration or narrowing of the vascular lumen.[1] Ultrastructurally, 'diabetiform' vascular changes are observed, including lamellation of the capillary and mesothelial basement membrane.[11–14] These changes raise the possibility that the presence of glucose in conventional PD solutions may be mediating these deleterious effects. Similar changes have been reproduced in animal models exposed to hypertonic, glucose-based dialysate.[15]

Moreover, glucose also has a dose-dependent inhibitory effect on mesothelial cell proliferation in human and animal models.[16–19] This toxicity may be mediated by oxidative stress.[18] Mitochondrial DNA damage has been demonstrated on exposure of human peritoneal mesothelial cells (HPMCs) to glucose.[20] Compared with other hyperosmolar solutes such as mannitol and glycerol, the inhibitory effects of glucose on mesothelial cells seems to be greater, implying both an effect of hyperosmolality and an intrinsic toxic effect of glucose on mesothelial cell proliferation.[21] Evidence that these glucose-induced structural changes translate into adverse effects on membrane function stems from a single-center observational cohort study by Davies *et al.*[22] In this study, patients with greater early and cumulative exposure to higher glucose concentrations experienced more rapid increases in small-solute permeability and faster deterioration of membrane function. However, the possibility that the need for higher dialysate glucose exposure may have been in response to declining RKF or to inadequate peritoneal UF, in the face of worsening peritoneal membrane function, cannot be excluded.

### Glucose degradation products

In 1986, the observation by Henderson *et al.*[23] that PD infusion pain correlated with the shelf life of the PD solution being infused ultimately gave rise to the discovery of GDPs in conventional PD solutions. The shelf life of the conventional dialysis solutions was found to correlate with increasing GDP content, as detected by photospectrometric analysis.[23] Since that time, increasing evidence from *in vitro* and animal studies suggests that the local toxicity of glucose may be, in part, related to the presence of GDPs in conventional PD solutions.

To date, the majority of evidence surrounding the peritoneal toxicity of GDPs has focused on the effects of GDPs on mesothelial cell injury.[24] Only a few of these low-molecular-weight aldehydes have been identified, with several more GDPs visible by high-performance liquid chromatography.[7] Initial reports suggested that the acute cellular toxicity due to GDPs was only achievable at high concentrations, exceeding those found in PD fluids.[25–27] However, the discovery of the GDP, 3,4-dideoxyglucosone-3-ene (3,4-DGE), confirmed that concentrations of 3,4-DGE found in conventional PD fluid could induce acute cellular toxicity using an *in vitro* fibroblast culture model.[28] Given the nature of the cell lines used and the short duration of incubation in previous studies ($<72$ h), specific conclusions regarding *in vivo* long-term peritoneal effects remained limited.

Using a culture of omental-derived HPMCs, Witowski *et al.*[24] demonstrated that exposure to six GDPs in concentrations typically found in conventional PD solution was not associated with short-term toxicity. However, after 6 weeks of exposure, the viability and function of the HPMCs was severely comprised. It would appear that not all GDPs have an equivalent capability for mesothelial cell toxicity.[29] 3,4-DGE has been shown to be among the most inhibitory for mesothelial cell proliferation, and is also the only GDP that has been demonstrated to enhance apoptosis of both peripheral leukocytes as well as renal tubular epithelial cells.[29–31] In addition, 3,4-DGE and formaldehyde are among the most potent GDPs responsible for impairment in mesothelial cell repair in response to injury.[32]

GDP-induced mesothelial cell injury and apoptosis also lead to intracellular hydrogen peroxide production and free radical formation, which may be important inciting events for peritoneal membrane inflammation and injury.[33,34] Moreover, GDPs have been shown to directly induce production of the profibrotic cytokine transforming growth factor-β and to stimulate vascular endothelial growth factor (VEGF) synthesis in HPMCs.[35–39] These two signaling molecules are thought to have key roles in the progressive peritoneal membrane fibrosis and vascular proliferation seen in long-term PD patients.[40] In a rat model, exposure to GDPs has also been shown to stimulate excessive proliferation of mesenchymal-like cells.[41] These cells may be derived through epithelial–mesenchymal transition (EMT), whereby peritoneal mesothelial cells undergo transition to a fibroblast-like phenotype and is thought to be a key mediator of peritoneal fibrosis.[42] Whether or not proliferation of mesenchymal cells is directly stimulated by exposure to GDPs or indirectly by GDP-induced upregulation of transforming growth factor-β (a known stimulus for EMT) is unclear.[42] Dialysate effluent obtained from patients at 12 months after the initiation of PD using low-GDP solutions contained fewer fibroblast-dominant cells compared with the effluent obtained from patients using conventional PD solutions, suggesting GDP-induced EMT *in vivo*.[43] Taken together, *in vitro* and animal data suggest that peritoneal mesothelial cell integrity may be adversely affected by the presence of GDPs in conventional PD solution. The alterations in mesothelial cell viability may initiate a cascade of events, leading to progressive peritoneal membrane injury.

### Advanced glycosylation end products

Under conditions of elevated glucose, advanced glycosylation end products (AGE) are formed from the non-enzymatic glycosylation of proteins.[44] AGEs have the potential to increase vascular permeability by disruption of the vascular basement membrane due to protein cross-linking to basement membrane components[45] or by the activation of the receptor for AGEs (RAGE) on endothelial cells.[46]

*In vitro* kinetic studies suggest that the formation of AGEs on exposure to conventional PD solutions appears to be largely mediated by the presence of GDPs.[47] GDPs appear to have greater reactivity than glucose in the formation of AGEs and incubation with $NpHL_{GDP}$ PD solutions results in lower systemic AGE levels compared with conventional PD solutions incubated at similar concentrations of glucose.[48,49] Moreover, in peritoneal effluent, AGEs have been detected at levels greater than plasma, and appreciable staining for AGEs has been demonstrated in the peritoneal membrane as early as within the first 3 months of PD therapy.[50,51]

Rat models suggest that accelerated AGE formation may have a causative role in PD solution-induced peritoneal membrane injury.[52] In these models, increased peritoneal deposition of GDPs and AGEs and upregulation of the RAGE are seen with exposure to conventional PD solutions compared with $NpHL_{GDP}$ solutions.[52] Structurally, these changes are accompanied by increases in submesothelial fibrosis, VEGF production, and microvascular proliferation, while functional changes include lower peritoneal UF.[52]

RAGE has also been detected on the surface of HPMCs.[53] Stimulation of RAGE by AGEs results in VEGF release by HPMCs, which leads to capillary tube formation of human umbilical vein endothelial cells in a co-culture model.[54] This may be an important mechanism underlying the angiogenesis of the peritoneal capillary network seen in long-term PD.[54] Moreover, AGEs binding to RAGE on HPMCs also stimulate activation and upregulation of vascular cell adhesion molecule-1 on the mesothelial cell surface.[55] Vascular cell adhesion molecule-1 has an integral role in facilitating leukocyte adhesion, which may activate an inflammatory pathway and lead to peritoneal injury.[56] Human peritoneal biopsies suggest that AGE accumulation in the peritoneal membrane occurs predominantly in the vessel wall. AGE deposition correlates with increased time on therapy and increased peritoneal permeability.[57–59]

### Dialysate pH and lactate

Topley *et al.*[60] investigated the effects of a lactate-buffered (pH 5.5) PD solution compared with a bicarbonate-buffered $NpHL_{GDP}$ PD solution on mesothelial cell toxicity using HPMCs. Toxicity was seen exclusively in HPMCs incubated with a lactat-buffered (pH 5.2) PD solution, but not when

incubated using a bicarbonate-buffered (pH 7.4) PD solution. However, it is possible that the difference in GDP content between the two solutions was likely largely responsible for the overall difference in mesothelial cell function between the two groups.

In addition to pH, the choice of buffer, lactate versus bicarbonate, appears to have an effect on HPMC metabolism, irrespective of the osmotic agent used. Plum *et al.*[61] compared HPMCs incubated at equivalent pH (7.4), but with varying buffers (lactate versus bicarbonate) and osmotic agents (glucose, amino acid, or glucose polymer solutions). Independent of the osmotic agent, there was no difference in the cell viability of HPMCs (using cytofluorometry to measure apoptotic and necrotic cells) between lactate versus bicarbonate-cultured HPMCs. However, 'superior' parameters of cell metabolism (improved interleukin-6 (IL-6) release and ATP production) were demonstrated in the bicarbonate, but not the lactate-incubated HPMCs. The effect appeared to be independent of the osmotic agents used in the culture medium.

More recently, Ogata *et al.*[62] have demonstrated that reduced HPMC metabolism (as measured by mitochondrial activity) in lactate-incubated HPMCs, compared with bicarbonate-incubated HPMCs, is accompanied by higher levels of basic fibroblast growth factor in the supernatant of HPMCs. Moreover, the higher levels of basic fibroblast growth factor in the lactate-buffered supernatant led to a greater degree of activation of human umbilical vein endothelial cells and human peritoneal fibroblasts. These findings suggest that the use of lactate may lead to reductions in mesothelial cell metabolism and viability, while increasing basic fibroblast growth factor production and local activation of endothelial cells and fibroblasts. The use of bicarbonate may abrogate these effects, translating into *in vivo* effects of reduction in neovascularization and fibrosis of the peritoneal membrane.

In addition to mesothelial cell toxicity, reduced dialysate pH and use of lactate in conventional PD solutions may lead to impaired peritoneal leukocyte function, compromising local peritoneal host defenses. The phagocytic index for bacteria was reduced when phagocytes were exposed to an intraperitoneal pH of 5 compared with 7 (ref. 63). During the lowest intraperitoneal pH at the initial phase of the PD exchange, peritoneal macrophage function appears to be transiently depressed, recovering over time as intraperitoneal pH increases. Intracellular acidification and influx of lactate from conventional PD solutions is likely responsible for the inhibitory effect on peritoneal macrophages.[64] Evaluation of a bicarbonate/lactate-based PD solution, compared with lactate-based solution, demonstrated that exposure to the bicarbonate/lactate-based neutral pH fluid led to improvement in peritoneal macrophage function, as measured by increased tumor necrosis factor-α production.[65,66] Similarly, these findings were recapitulated using a lactate-based, but low-GDP neutral pH solution that demonstrated improved peritoneal leukocyte survival and respiratory burst responses.[67] However, given that GDPs have been shown to promote peripheral leukocyte apoptosis,[31] a lower GDP content may have been partially responsible for the improvement in peritoneal macrophage function in the bicarbonate solution. Therefore, it is likely that the improvements in peritoneal leukocyte function are due to the combined effects of the buffer used, the effects of increased intraperitoneal pH, and the effects of the lower GDP content in the neutral pH solution. Moreover, whether or not the *in vitro* cytotoxicity of dialysate pH at levels present in conventional PD solutions similarly leads to *in vivo* cytotoxicity is not known. It is possible that the *in vivo* cytotoxicity of dialysate pH may be attenuated, given that dialysate pH is depressed only for the first 10–30 min of an exchange, reaching a pH level that is similar to serum levels after that time.

## BIOMARKERS OF 'BIOCOMPATIBILITY'

Although *in vitro* and animal data suggest that the constituents of current conventional PD solutions contribute to significant local peritoneal toxicity, confirmatory human data is lacking, owing to the challenges in obtaining serial

**Table 2 | Dialysate effluent markers in the evaluation of the biocompatibility of low-GDP neutral pH peritoneal dialysis solutions**

| | | | | | Dialysate effluent markers (relative to conventional PD solutions) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Study type | F/U (months) | Solution type | *N* | CA-125 | VEGF | IL-6 | TGF-β | TNF-α | HA | PICP |
| Kim *et al.*[75] | RCT | 12 | Balance | 69 | ↑ | — | ↔ | — | — | — | — |
| Choi *et al.*[78] | RCT | 12 | Balance | 104 | ↑ | — | — | — | — | — | — |
| Rippe *et al.*[77] | RCT | 24 | Gambrosol Trio | 80 | ↑ | — | — | — | — | ↓ | ↑ |
| Haag-Weber *et al.*[76] | RCT | 20 | Gambrosol Trio | 69 | ↑ | — | — | — | — | — | — |
| Cooker *et al.*[8] | RCT | 6 | Physioneal | 92 | — | ↔[a] | ↓ | — | ↔ | — | — |
| Szeto *et al.*[82] | RCT | 12 | Balance | 50 | ↑ | — | — | ↔ | — | ↓ | — |
| Fusshoeller *et al.*[80] | Randomized crossover | 5 | Physioneal | 12 | ↑ | — | ↓ | — | — | — | — |
| Haas *et al.*[79] | Randomized crossover | 3 | Balance | 40 | ↑ | ↔ | — | ↔ | — | — | — |
| Williams *et al.*[81] | Randomized crossover | 6 | Balance | 71 | ↑ | ↔ | — | — | ↔ | ↓ | ↑ |
| Zeier *et al.*[48] | Randomized crossover | 4 | Gambrosol Trio | 21 | ↑ | — | — | — | — | — | — |

Abbreviations: CA-125, cancer antigen 125; F/U, follow up; GDP, glucose degradation product; HA, hyaluronic acid; IL-6, interleukin 6; PD, peritoneal dialysis; PICP, procollagen peptide; RCT, randomized controlled trial; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.
[a]Significant difference at 3 months, but not at the end of follow-up.

peritoneal membrane biopsies in patients while undergoing PD therapy. Therefore, the majority of *in vivo* evidence largely stems from the measurement of dialysate effluent markers (Table 2). The utility of surrogate markers such as dialysate cancer antigen-125 (CA-125), VEGF, and IL-6 for the health and viability, and the inflammatory status of the resident cells of the peritoneum is reviewed below.

#### Cancer antigen-125

CA-125 is a glycoprotein constitutively produced by mesothelial cells, and is, therefore, a putative marker of mesothelial cell mass and function.[68–70] Declining dialysate effluent CA-125 levels are seen with time on PD.[71–74] These findings support the histological findings of progressive loss of mesothelial cell mass that have been observed with time on PD.[1] Across multiple studies, it has been established that dialysate CA-125 levels are higher with the use of $NpHL_{GDP}$ solutions compared with conventional PD solutions[48,75–82] (Table 2). Interestingly, many of these studies, including a recent study by Kim *et al.*[75] and the Euro-Balance trial, have shown that during the short period of observation, levels of CA-125 in patients treated with $NpHL_{GDP}$ solutions rise over time, whereas levels of CA-125 remain stable in patients treated with conventional PD solutions.[81] In the Euro-Balance trial, after exposure to $NpHL_{GDP}$ PD solution for only 12 weeks, levels of CA-125 increased three- to four-fold.[81] In both studies, however, it is not clear whether the increase in CA-125 reflects increased mesothelial cell mass or greater synthesis per remaining mesothelial cell. In a prospective observational study of 110 incident patients followed up for at least 1 year, there were no longitudinal changes in dialysate CA-125 levels over time compared with baseline. Moreover, dialysate effluent CA-125 levels were not different between 55 patients treated with conventional PD solutions and 55 patients treated with $NpHL_{GDP}$ PD solutions.[83]

In the absence of studies examining the relationship between effluent CA-125 levels and peritoneal membrane morphology and function, alternative explanations exist. CA-125 levels can increase in the face of inflammatory stimuli such as peritonitis, in which the elevated dialysate effluent CA-125 levels result, in part, from CA-125 release from necrotic mesothelial cells.[84] After recovery, effluent CA-125 levels appear to be similar to controls.[84] In the study by Kim *et al.*,[75] one cannot exclude the possibility that elevated CA-125 levels in the group treated with $NpHL_{GDP}$ solutions may have been, in part, related to low-grade intraperitoneal inflammation. The resultant increase in effluent CA-125 levels in the group of 48 incident patients treated with a $NpHL_{GDP}$ PD solution was accompanied by a statistically significant decrease in serum albumin, an increase in small-solute transport, and a trend to increased serum C-reactive protein relative to the 43 incident PD patients treated with conventional PD solutions at 13 months. Moreover, in a study by Oh *et al.*,[85] effluent CA-125 levels were strongly associated with the dialysate appearance of albumin, which has been independently associated with systemic and peritoneal membrane inflammation. Given that few long-term, prospective, multicenter clinical studies have validated the prognostic significance of effluent CA-125 levels on clinical outcomes in PD patients, the utility of dialysate CA-125 as a surrogate marker of peritoneal membrane health and integrity may be limited.

#### Vascular endothelial growth factor

VEGF is produced by a wide range of human cell lines and stimulates nitric oxide synthase activity, vascular permeability, and angiogenesis.[86,87] The capacity for local production of VEGF in the human peritoneum stems from documentation of VEGF synthesis in both HPMC culture and in animal models.[40,88,89] Moreover, *in vivo* and *in vitro* findings suggest that mesothelial cells that have undergone EMT have the capacity to synthesize VEGF.[90] In humans, production of VEGF in the peritoneal endothelium increases with time on PD, and is accompanied by increase in vascular density.[91] Functionally, in humans, higher dialysate effluent VEGF levels have been associated with increased peritoneal small-solute and macromolecular permeability, likely a reflection of an increase in the peritoneal vascular surface area.[92,93] A causal basis for this association stems largely from animal data, in which local administration of VEGF appears to induce peritoneal microvascular changes that are partially reversible on treatment with anti-VEGF monoclonal antibodies.[40]

VEGF production by HPMCs appears to be stimulated by proinflammatory cytokines and by AGEs such as glycated albumin, and not by glucose itself.[88] In animal models, effluent VEGF levels, peritoneal VEGF staining, and angiogenesis appear to be reduced with intraperitoneal administration of $NpHL_{GDP}$ solutions, compared with those treated with conventional PD solutions.[52] In humans, the impact of $NpHL_{GDP}$ solutions on effluent levels has been examined in several studies[81,94,95] (Table 2). The majority of these studies have not demonstrated appreciable differences in effluent VEGF levels in those treated with either solution. As is the problem with many dialysate effluent biomarkers, it is possible that effluent VEGF levels may not be entirely reflective of local peritoneal production, given that transperitoneal transport of VEGF from the systemic circulation to the dialysate has been described.[96] Moreover, dialysate effluent VEGF levels are a reflection of total VEGF production by all resident cells of the peritoneum. It is possible that $NpHL_{GDP}$ solutions affect VEGF production differently across various cell types (that is, mesothelial cells, fibroblasts, and endothelial cells).

#### Interleukin-6

Mesothelial cells are the major source of intraperitoneal IL-6 synthesis.[97] Evidence for local IL-6 production stems from effluent levels, which are several fold higher than serum levels.[92] HPMCs secrete IL-6 in response to spent peritoneal dialysate, tumor necrosis factor-$\alpha$, and IL-1$\beta$.[97] Dialysate

effluent levels of IL-6 are associated with baseline peritoneal transport status and downstream inflammatory factors such as membrane chemoattractant protein-1, angiogenic factors such VEGF, as well as adhesion molecules (that is, vascular cell adhesion molecule-I, intercellular adhesion molecule-I), suggesting that IL-6 may have a role in the initial induction of peritoneal membrane inflammation.[85] In the absence of IL-6 receptors on mesothelial cells, activation of HPMC is largely mediated by trans-signaling with peritoneal leukocyte-mediated release of the soluble IL-6 receptor and activation of the gp130 receptor on HPMCs by the soluble IL-6/IL-6 complex.[98]

However, IL-6 also has anti-inflammatory effects, inducing downregulation of inflammatory cytokines by activation of IL-1 and tumor necrosis factor receptor antagonists. Further confusing the role of IL-6 is the reported positive association between dialysate effluent IL-6 levels and dialysate effluent CA-125 levels, a putative marker of mesothelial health and integrity.[85] Although some studies suggest that effluent IL-6 levels are reduced with treatment with $NpHL_{GDP}$ solutions, this has not been confirmed by other studies[75,80] (Table 2). Until the role of IL-6 in progressive peritoneal membrane injury as well as its predictive value in assessing clinically meaningful end points has been fully elucidated, its use as a biomarker of biocompatibility will remain limited.

## SYSTEMIC EFFECTS OF GDPS AND AGES

In diabetes, the vasculotoxicity of AGEs has been well established and has been linked with the development of both microvascular complications and accelerated atherosclerosis.[99] Moreover, diabetic patients with ESRD have almost twofold AGE deposition in systemic arterial walls compared with diabetic patients without renal disease.[100] Importantly, and not often appreciated, plasma levels of AGE in HD patients appear to be similar, if not higher, compared with those seen in PD patients.[101] Taken together, this would suggest that uremia itself is independently associated with elevated systemic AGE levels, irrespective of dialysis modality.

Whether or not the use of a $NpHL_{GDP}$ solution compared with the use of conventional glucose-based lactate-buffered solution can result in less systemic AGE formation was tested in the Euro-Balance study.[81] Serum AGE levels of carboxymethyllysine and imidazolone were measured in a subset of study patients. In patients treated with the low-GDP solution, local effluent levels of carboxymethyllysine and imidazolone were unchanged, compared with treatment with the conventional PD solution, but systemic serum levels of both GDPs fell significantly compared with baseline values over a 12-week period. It should be noted that absolute levels of serum imidazolone remained relatively unchanged between the two groups.

These results suggest that exposure to a $NpHL_{GDP}$ PD solution may lead to decreased systemic levels of some, but not all, AGEs. The clinical significance of these findings needs to be interpreted in the context of the Euro-Balance study design. Only two known AGEs were measured. There was a relatively short duration of observation (24 weeks), with the measurement of AGEs in only a subset of patients. In this study and in others, no correlation could be demonstrated among circulating plasma AGE levels, tissue AGE deposition, and clinical outcomes. Moreover, in HD patients, the demonstration that elevated plasma levels of carboxymethyllysine are associated with a survival advantage calls into question the prognostic significance of elevated levels of serum AGE in PD patients.[102]

## CLINICAL OUTCOMES USING LOW-GDP, NEUTRAL pH PD SOLUTIONS

### Peritonitis

Local peritoneal immunity has an important role in the prevention and resolution of PD peritonitis. When exposed to conventional dialysate, however, there is abnormal leukocyte recruitment in response to inflammatory stimuli[103] and impaired phagocytic function.[104]

Given that impaired peritoneal immunity is thought to be, in part, due to the bioincompatibility of the conventional dialysis solutions used, several studies have sought to determine whether the $NpHL_{GDP}$ PD solutions might be associated with improved peritoneal immune function. In a small, randomized crossover study, the use of $NpHL_{GDP}$ dialysate for 6 months was associated with enhanced phagocytic activity of peritoneal macrophages.[80] Another small, randomized crossover study showed an increase in the number of peritoneal effluent macrophages after 3 months of exposure to $NpHL_{GDP}$ solutions.[105]

Several observational studies have sought to assess whether these differences in markers of peritoneal immunity translate into reduced peritonitis risk, with conflicting results. The largest of these studies was a retrospective cohort study of 1909 incident Korean patients on CAPD between 2002 and 2005.[106,107] Although patient survival was greater among the patients treated with the $NpHL_{GDP}$ solutions (see later), there was no difference in peritonitis-free survival or peritonitis rate.[106,107] In contrast, in a study by Ahmad *et al.*[108] from 2002 to 2004, the peritonitis rate was significantly lower among patients using $NpHL_{GDP}$ solutions (1 in 52.5 patient-months versus 1 in 26.9 patient-months). Another observational study comparing peritonitis rates in 100 incident CAPD patients treated with either conventional or $NpHL_{GDP}$ solutions similarly found a lower peritonitis rate among those using the latter.[109] Results are supported by a third study in which 67 patients treated with conventional PD solutions from 1990 to 1999 were compared with 53 patients treated with a $NpHL_{GDP}$ solution from 2000 to 2005, with the latter group having a lower peritonitis rate.[110]

The basis for the conflicting results of these observational studies may relate to residual confounding between the conventional and $NpHL_{GDP}$ PD solution groups. As patients in these studies were not randomized to one or other treatment, it is possible that patients receiving $NpHL_{GDP}$ PD solutions differed in several respects, including their under-

**Table 3 | Clinical outcomes using low-GDP neutral pH PD solutions: peritoneal membrane**

| Study | N | Follow-up | Population | Design | Solution | RKF[a] | Daily UF | Small-solute transport | Peritonitis |
|---|---|---|---|---|---|---|---|---|---|
| Williams *et al.*[81] | 86 | 24 Weeks (12/12) | Prevalent | Multicenter/crossover RCT | Balance | ↑ | ↓ | ↑ | ↔ |
| Fan *et al.*[112] | 93 | 1 Year | Incident APD/CAPD | Single-center RCT | Physioneal/balance | ↔ | ↔ | ↔ | ↔ |
| Choi *et al.*[78] | 104 | 1 Year | Prevalent CAPD | Single-center RCT | Balance | ↔ | ↑ | ↔ | NR |
| Montenegro *et al.*[118] | 36 | 1 Year | Incident CAPD | Prospective observational | Bicavera | ↑ | ↓ | ↔ | NR |
| Szeto *et al.*[82] | 50 | 1 Year | Incident CAPD | Single-center RCT | Balance | ↔ | ↔ | ↔ | ↔ |
| Kim *et al.*[75] | 91 | 1 Year | Incident CAPD | Multicenter RCT | Balance | ↑ | ↓ | ↑ | ↔ |
| Haag-Weber *et al.*[76] | 69 | 20 Months | Incident/prevalent CAPD[b] | Multicenter RCT | Gambrosol Trio | ↑ | —[c] | —[c] | ↔ |

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; GDP, glucose degradation products; NR, not reported; PD, peritoneal dialysis; RCT, randomized controlled trial; RKF, residual kidney function; UF, ultrafiltration.
[a]Residual kidney function, as measured by the mean of 24-h collection for urea and creatinine clearances standardized for body surface area.
[b]Four patients were treated with automated peritoneal dialysis.
[c]Daily ultrafiltration not corrected for overfill and data not provided for peritoneal small solute transport.

lying comorbidities or other aspects of their PD therapy that could have influenced peritonitis risk. This latter issue is particularly relevant in studies comparing patients across eras, as those receiving $NpHL_{GDP}$ solutions are more contemporary cohorts that are known to have lower peritonitis rates.[111] There are only two randomized trials to date of conventional versus biocompatible PD fluids that included data on infectious outcomes (Table 3).[76,112] In the first of these studies, Fan *et al.*[112] randomized 93 incident PD patients to conventional or $NpHL_{GDP}$ PD solutions for 1 year, with RKF as the primary end point and peritonitis as a secondary end point. There were no significant difference in the peritonitis rates. Similarly, Haag-Weber *et al.*[76] randomized 80 patients to standard or $NpHL_{GDP}$ dialysate for 18 months. Although peritonitis was not their primary end point, there was no difference in peritonitis risk between the groups. Although neither of these studies was powered for the outcome of peritonitis, there was no suggestion of benefit of the newer solutions, with respect to peritonitis risk. Further randomized controlled studies powered to study the occurrence of peritonitis with different PD solutions are required to clarify whether improvements in putative markers of peritoneal immunity translate into reduced peritonitis risk.

### Peritoneal membrane function

UF failure remains one of the major sources of late technique failure for patients on PD.[113] Longitudinal changes in peritoneal membrane function include increases in peritoneal membrane small-solute permeability and reduction in peritoneal UF capacity.[114] If the use of $NpHL_{GDP}$ PD solutions could slow or reverse these changes, then it is possible that their use could translate into clinically meaningful outcomes.

Several studies using $NpHL_{GDP}$ PD solutions have suggested no improvement in peritoneal UF or longitudinal differences in peritoneal small-solute permeability[36,50,69,86,93,104] (Table 3). In fact, several recent studies have demonstrated that use of $NpHL_{GDP}$ solutions is associated with reduction in peritoneal UF, which may be partially explained by an accompanying increase in small-solute permeability.

Interpretation of these studies is limited for several reasons. In all the studies, peritoneal membrane function was not studied as a primary end point. Several studies were limited by non-randomized treatment allocation. In the study by Kim *et al.*,[75] baseline small-solute transport characteristics were not provided, and so follow-up measures may reflect case mix differences between the groups at baseline. Moreover, selection bias of patients with a tendency to relatively better preservation of peritoneal membrane function may have occurred in several studies. This may be the result of recruitment of prevalent patients and the effects of informative censoring, leading to absence of longitudinal values on peritoneal membrane function in patients who died or were transferred to HD. The relatively short follow-up of these studies (majority $<1$ year) makes it difficult to extrapolate the impact of low-GDP solutions on peritoneal membrane function beyond 1–2 years of PD therapy. Lastly, the variability of PD solutions across studies in terms of the buffer, GDP content, and co-intervention in some study protocols with the use of non-glucose-based PD solutions, further limit conclusions regarding their impact.

### Residual kidney function

Across observational studies, the preservation of RKF is a consistent and potent predictor of patient survival in both PD and HD patients.[115,116] Therefore, strategies aimed at RKF preservation represent an important therapeutic target in the management of PD patients. The ability of GDPs to promote renal tubular apoptosis in cell culture, coupled with the established role of AGEs in the induction of glomerulosclerosis and progression of diabetic nephropathy, has led to the hypothesis that the use of a $NpHL_{GDP}$ solution may be associated with better preservation of RKF compared with traditional PD solutions.[30,117] The Euro-Balance and several other studies have purported to demonstrate better preservation of RKF (Table 3).[75,76,78,81,82,118] Moreover, results from Montenegro *et al.*,[118] using a pure bicarbonate PD solution, supported these findings. In both studies, and in the recent study by Kim *et al.*,[75] the resultant improvement in RKF was accompanied by a statistically significant decrease in

peritoneal UF. This may have been, in part, the driving source for the higher RKF seen, reflecting differences in volume status during treatment between traditional and biocompatible PD solutions. Both studies were crossover trials with a short duration of follow-up, limiting the interpretation of the findings. A recent, well-powered, randomized controlled trial by Fan *et al.*[112] refuted these findings. With RKF as the primary end point, this study did not demonstrate a benefit with the use of biocompatible (bicarbonate/lactate) solutions on RKF preservation in a group of 93 PD patients. Similar findings were also noted by Szeto *et al.*[82] using the same solutions as in the Euro-Balance trial. A recent multicenter randomized controlled trial comparing a lactate-based low-GDP PD solution with a conventional PD solution revealed a slower rate of RKF decline in the group receiving the low-GDP solution.[76] However, unlike most studies, RKF decline was modeled exponentially rather than linearly as in most studies to date, and no information was provided on peritoneal membrane function throughout the study.

The basis for the conflicting study results may, in part, reflect the different solutions used, each with its own profile of potentially glomerulotoxic and vasculotoxic GDPs. In addition, the studies included a heterogeneous mix of both incident and prevalent PD patients. Finally, the contribution of reduced UF and relative volume overload with the newer solutions confuses the issue even more. In the absence of further prospective studies, definitive conclusions regarding the impact of biocompatible solutions on RKF preservation cannot be drawn.

### Survival

Most clinical studies of biocompatible solutions have focused on outcomes such as peritonitis, RKF, and peritoneal membrane function. Only two studies to date have sought to identify whether the use of biocompatible solutions is associated with improved patient survival. The first of these two studies by Lee *et al.*[106] was a prospective, longitudinal observational cohort study of 1909 Korean PD patients followed up between 2002 and 2005. Although no difference in technique survival was observed between groups, there was higher patient survival among those who received the biocompatible solutions relative to conventional solutions in the multivariable model. This was followed by an extension of the first study to include an observational cohort study of Korean PD patients followed up between 2003 and 2006.[119] Again, there were significant baseline differences in patient characteristics between those using biocompatible solutions versus conventional solutions. After propensity matching and multivariable adjustment, patient survival was better among patients using the biocompatible solutions, with a hazard ratio of 0.7. Of concern, outcomes were assessed in the first study appropriately by an 'intention-to-treat' model, whereas in the extended study this was not done, so that the healthier patients switched from conventional to new solutions were simply removed from the analysis.

Although the results of these studies are interesting, it is difficult to avoid the issue of residual confounding using these observational data sources. For example, although some important covariates were adjusted for in both studies, others such as more detailed patient comorbidities, RKF, inflammatory status, and era of solution use were not. Furthermore, both studies included only Korean PD patients and the second study included patients with very low cardiovascular morbidity, such that the observed findings may not be generalizable. As with all of the aforementioned clinical outcomes, the only way to definitively answer whether biocompatible solutions impart a survival advantage would be to do a large, multicenter randomized controlled trial.

## CONCLUSION

There is a growing literature to support the relative bioincompatibility of conventional dialysate, as well as the link between these unphysiological conditions and alterations in peritoneal membrane morphology and function. This has led to the use of $NpHL_{GDP}$ solutions in an attempt to better preserve the peritoneal membrane among patients on long-term PD. Although there is biological plausibility and *in vitro* and animal data to suggest potential benefit of these newer solutions, consistent clinical outcome data are lacking. Surrogate markers of biocompatibility should be viewed with caution, and careful validation against important clinical end points are needed before their adoption as study end points.

Studies to date have largely been observational in nature, and have examined surrogate clinical outcomes including RKF and peritoneal membrane function. Most published randomized controlled trials have been relatively small, single-center studies and, therefore, underpowered to detect clinically meaningful differences. Future multicenter studies are required that recruit patients from multiple continents and focus on clinically relevant solid end points, including peritonitis, technique, and patient survival. Furthermore, significant differences in both the profile and the absolute concentration of GDPs in available $NpHL_{GDP}$ solutions exist, and this is often not accounted for when comparing studies. These issues have led to conflicting results and much confusion in trying to interpret the literature. Given the incremental cost associated with the long-term use of $NpHL_{GDP}$ solutions, further study is warranted before biocompatible solutions can be considered the standard of care in the management of PD patients.

## DISCLOSURE

All the authors declared no competing interests.

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